

DOCKET NO: 283723US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :  
RAMON MERCE VIDAL ET AL : EXAMINER: RAIMANI, N  
SERIAL NO: 10/566,403 :  
FILED: AUGUST 11, 2006 : GROUP ART UNIT: 1625  
FOR: INDOL-7-SULFONAMIDE :  
DERIVATIVES, THEIR PREPARATION  
AND THEIR USE 5-HT-6 AS  
MODULATORS

DECLARATION UNDER 37 C.F.R. §1.132

COMMISSIONER FOR PATENTS  
ALEXANDRIA, VIRGINIA 22313

SIR:

I Xavier Codony-Soler state that:

I am the named inventor of this application.

I understand that the U.S. Patent Office has rejected certain claims of this application for lack of description pertaining to the use of the sulfonamide compounds of formula (I) for regulating 5-HT<sub>6</sub> receptors and for the treatment and/or prevention of diseases and/or disorders related to this 5-HT<sub>6</sub> receptor regulation.

The following experiments were performed by me or under my direct supervision and control.

The role and thus the correlation of the 5-HT<sub>6</sub> receptor in the diseases and disorders in the application was known in the field prior to the filing date of the application. This is already described in paragraphs [0003] to [0006] of the application.

The application also describes that the compounds of formulae Ia, Ib and Ic have affinity for the 5-HT<sub>6</sub> receptor (see [0009]).

The affinity of 5-HT<sub>6</sub> receptor and those compounds is further confirmed by the affinity data presented below.

The Experiments were performed in accordance with the description provided in paragraph [0103] with the following further details:

[<sup>3</sup>H]-LSD binding was assayed in a reaction mixture containing 50 mM Tris-HCl, 10 mM MgCl<sub>2</sub>, 0.5 mM EDTA buffer (pH 7.4), and generally 2.7 nM [<sup>3</sup>H]-LSD, (final vol. 200 µl). The incubation was initiated by the addition of the membrane suspension, (≈ 22.9 µg membrane protein), and allowed to continue at 37°C for 60 min. Incubation was terminated by rapid filtration with a Brandel cell harvester through glass fiber Whatman GF/B filters pre-wet with polyethylenimine 0.5 %. The filters were washed three times with three ml of buffer Tris-HCl 50 mM pH 7.4. Filter sections were transferred to minivials and 5 ml of Ecoscint H liquid scintillation cocktail was added to each vial. Vials were allowed to set for several hours prior to counting on a Wallac Winspectral 1414 liquid scintillation counter. Nonspecific binding was determined in the presence of 100 µM serotonin and assays were performed in triplicate.

The membranes expressing human 5-HT<sub>6</sub> serotonin receptor were obtained from PerkinElmer Life and Analytical Sciences, Boston, USA. (for product information: [http://las.perkinelmer.com/content/technicalinfo/dts\\_es-316-m400ua.pdf](http://las.perkinelmer.com/content/technicalinfo/dts_es-316-m400ua.pdf)).

The results are shown in the Table below

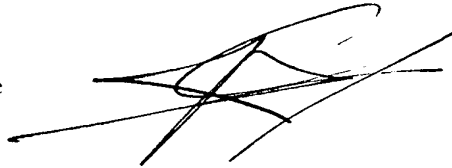
Table 1. 5-HT <sub>6</sub> receptor Affinity Data	
Compound No.	IC <sub>50</sub> (μM)
1	34
3	50
6	43
8	9

The IC<sub>50</sub> is a measure of the displacement of the standard radiolabelled compound (in this case, [<sup>3</sup>H]-LSD) for the binding site of the receptor (in this case human Serotonin 5-HT<sub>6</sub>). The constant of inhibition for a drug (K<sub>i</sub>) is the concentration of competing ligand in a competition assay which would occupy 50% of the receptors if no radioligand were present. The K<sub>i</sub> is related to IC<sub>50</sub> following the formula:  $K_i = IC_{50} / (1 + (S/K_d))$ , where S is radioligand concentration and K<sub>d</sub> is the affinity (dissociation constant) of the radioligand for the receptor. Whereas the IC<sub>50</sub> value for a compound may vary between experiments depending on radioligand concentration, the K<sub>i</sub> is in theory an absolute value.

5-HT<sub>6</sub> receptor has been involved in several brain disorders, based on experimental work performed in animal models, but also based on mRNA and protein expression in post-mortem human brains. The compounds have been tested for the affinity at the human 5-HT<sub>6</sub> receptor so an *in vivo* effect could be expected, although there are several factors like functionality at the receptor, pharmacokinetics and metabolism of the compound, and so on, that may modulate the final action of a particular compound in a particular disease state.

The undersigned declare further that all statements made herein are of her own knowledge are true and that all statements made on information are believed to be true. Further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Signature

A stylized, handwritten signature in black ink, consisting of several overlapping loops and a long horizontal stroke extending to the right.

Date

10th January 2008